membrane compartment. Thus, the principles discovered by this work could have broad implications for organization of cellular membrane systems.

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Retinal Processing: Global Players Like It Local

A recent study of a specific type of retinal amacrine cell shows how a single interneuron can implement a large number of parallel feedback circuits, illustrating how highly complex circuits can be generated by a small number of neurons.

Timm Schubert and Thomas Euler

Not too many years ago, the canonical textbook neuron could be quickly summarized: it integrated synaptic input received by its dendrites, applied a threshold and, depending on the result, in an all-or-nothing fashion, generated a spike that ran along its axon to the next neuron(s) in the network. Today, we know that neurons are complex and extremely diverse structures [1,2]: they can contain multiple processing units that perform complicated computations in parallel, with different degrees of interaction. In a recent study, Grimes and co-authors [3] dissected the biophysical mechanisms that allow such parallel processing in a single neuron, using the example of a retinal interneuron that takes this to an extreme. By combining electrophysiology, two-photon calcium imaging and modeling, they elegantly demonstrate that a single A17 amacrine cell in the rat retina provides the retinal circuitry with more than a hundred local feedback units that — under certain conditions — act largely independently.

With up to 40 morphologically distinct types, amacrine cells are the largest class of retinal interneurons [4] (Figure 1). Many lack dedicated output structures, such as an axon, and their dendrites serve both to receive and relay synaptic input and output, respectively. Amacrine cells may provide the neuronal 'hardware' for a substantial number of the computations performed by the retina; in view of this it is surprising that, to date, approximately 100 years after the morphological diversity of amacrine cells was first described, the function of only a few types is well understood. With a dendritic field diameter of approximately 400 μm in the rat retina, A17 cells belong to the subclass of wide-field amacrine cells, which are typically associated with tasks involving some sort of spatial or spatio-temporal interaction. For instance, 'polyaxonal' amacrine cells [5] connect distant regions of the retina and have been implicated in object segregation [6]. 'Starburst' amacrine cells compute the direction of image motion in their dendrites [7], with dendritic branches acting as largely independent detection units (reviewed in [8]). In contrast, Grimes *et al.* [3], describe a very local role for the A17 cell, in which its extended dendritic plexus subserves the formation of individual local feedback circuits with single bipolar cell axon terminals — rather than providing the substrate for surround inhibition, as previously discussed [9].

The morphology of the amacrine cell referred to as A17 in rat or cat [10,11], and as S2 in rabbit [12], is extremely well conserved across mammalian species: A17 cells extend dozens of rather thin dendrites bearing small varicosities, which form reciprocal GABAergic feedback synapses onto the axon terminals of rod-photoreceptor-selective bipolar cells. This characteristic morphology and straight-forward synaptic connectivity makes the A17 cell an attractive candidate for research of retinal signal processing; indeed, there have been a substantial number of A17 studies over the past couple of years [10,13,14]. Given their large dendritic field, it has been proposed that A17 cells mediate receptive field surround inhibition of rod bipolar cells [9,14,15]. This view has been challenged by Grimes *et al.* [3], who suggest that under low light conditions — the actual physiological working regime of the rod pathway — A17 cells are not

involved in receptive field surround generation by supplying spatially offset inhibition, but rather provide local gain control at the individual rod bipolar cell terminal [16]. The functional isolation of the A17 varicosities results from a combination of factors: First, the neurites connecting varicosities are very thin, which limits electrotonic signal spread. Second, the densities of voltage-activated sodium and potassium channels are balanced, such that membrane excitability is not enhanced. Third, the calcium dynamics in the individual varicosities particularly support local transmitter release.

The third of these mechanisms was the focus of an earlier study by the same group [13], which showed that calcium influx through bipolar-cell-activated glutamate receptors is amplified by calcium release from internal stores. This calcium is enough to drive reciprocal GABA release onto the bipolar cell terminal, without requiring the activation of voltage-gated calcium channels [17]. Thus, substantial membrane voltage changes that could easily propagate to neighboring varicosities and hamper isolation are avoided. Performing such localized independent feedback, rather than integrating broader spatial signals, is unexpected for such a large interneuron and encourages speculation about parallel functional processing units in other neuron types — not only in the retina but also in other parts of the brain.

The retina has to be sufficiently thin and optically transparent to prevent scattering of light as it passes through the tissue *en route* to detection. At the same time, multiple retinal microcircuits have to be repeated at every retinal location to preserve spatial acuity of the various retinal signaling pathways. Thus, the retina should particularly benefit from dendrites that perform local computations, while minimizing the required neuronal wiring volume and metabolic costs. As discussed in detail by Grimes *et al.* [3], A17 cells may well represent an optimized compromise that provides reasonably local feedback inhibition while minimizing wiring costs. Smaller and larger cells may be able to do the same job, but would require more precious space or run into metabolic transport problems, respectively. It is also possible that the A17 morphology supports additional functions, i.e. under different light

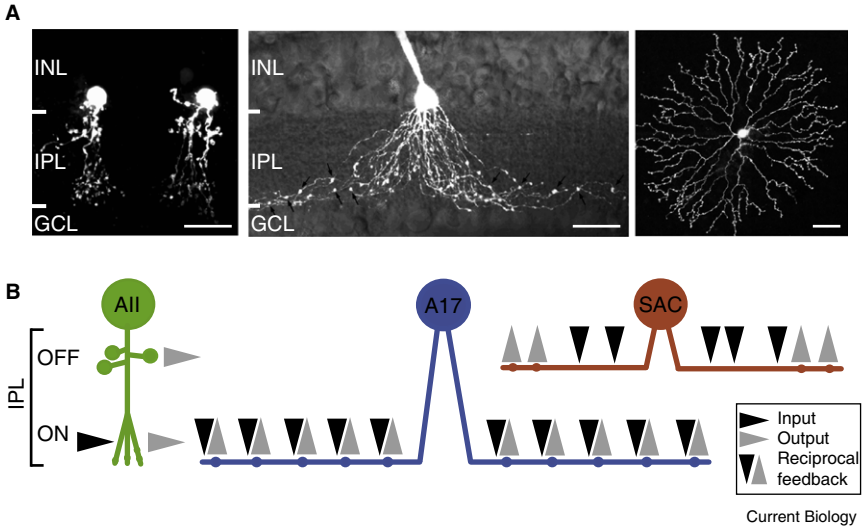

Figure 1. Morphologically distinct amacrine cells in the mammalian retina utilize different dendritic processing strategies.

(A) Variety of morphologically distinct amacrine cell types in the mammalian retina: two individually dye-injected AII amacrine cells in mouse retinal slice (left), an A17 amacrine cell in rat retinal slice (middle; from [3]), dye-filled starburst amacrine cell in the rabbit whole mount retina (right). INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. Scale bars = 25 μm. (B) Different dendritic processing strategies of amacrine cells. AII amacrine cells (green) receive synaptic input from rod bipolar cells in the ON-sublamina of the IPL and provide output to cone bipolar cells (not shown) in both the ON- and OFF-sublamina. A17 amacrine cells (blue) form local reciprocal feedback synapses with individual rod bipolar cell axon terminals (not shown). Starburst amacrine cells (red) receive synaptic input along their dendrites and provide output to other neurons via their distal dendrites.

conditions. Using a model derived from their data, Grimes *et al.* [3] suggest that an A17 branch can isolate synaptic events in different varicosities at photon fluxes typical for low-light (scotopic) conditions. With increasing light intensity (and photon flux), the probability of synchronous inputs to neighboring varicosities along a dendrite increases. This could then lead to interactions that enhance synaptic input. What functional role such varicosity interaction in A17 cells may play remains to be investigated.

A strict minimization of wiring costs, as suggested for A17 cells, may not always be possible (or desirable), as illustrated by the AII amacrine cells. AII cells are glycinergic, small-field amacrine cells that receive synaptic input from rod bipolar cells and relay rod signals via direct synaptic contacts with the axon terminals of cone bipolar cells to ON and OFF ganglion cells [18]. Thus, they integrate input from multiple rod bipolar cells and provide vertical signal transfer with (reasonably) high spatial acuity. To fulfill this particular function, these small interneurons are close to being electrically isotonic and accelerate synaptic output using voltage-gated sodium channels [19]. In this case, functionally subdividing a large neuron — as in the A17 cell — does not appear to be a viable option; and as a consequence, AII amacrine cells display the highest density of all amacrine cell types (with the corresponding high wiring costs).

In conclusion, variations in the complex interplay between a neuron's morphology, its active voltage conductances and properties like local calcium dynamics within dendritic compartments can lead to very different, sometimes completely unexpected forms of signal processing. In the case of the A17 cell, this interplay yields highly localized feedback inhibition. With 30 or so types of amacrine cells left to examine, it will be interesting to see what other secrets the retina still holds.

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Plasmodesmata Formation: Poking Holes in Walls with *ise*

Secondary plasmodesmata are cytoplasmic channels connecting adjacent plant cells that arise after cell division. How membrane-delimited channels penetrate cell walls is unknown, but now two genes, *ISE1* and *ISE2*, are shown to be required for pathways that limit their formation.

Dong-Keun Lee and Leslie E. Sieburth

Cell–cell communication is central for developmental decision making. In plants, an important vehicle for cell–cell communication is plasmodesmata. These channels provide a cytoplasmic bridge between adjacent cells; their structure, still under intense investigation, includes a centrally located desmotubule (a narrow strand of endoplasmic reticulum) surrounded by a cytoplasmic sleeve and attendant proteins, and bounded by plasma membrane (Figure 1A). Plasmodesmata carry out selective cell-to-cell trafficking of proteins and mRNAs as well as non-selective trafficking of small molecules, including nutrients and hormones (reviewed recently in [1,2]). Both types of transport are developmentally regulated. One element of regulation is the control of size exclusion limit. During plant development, sets of coupled cells (called symplastic domains) are dynamically regulated [3–8]. However, the biogenesis of plasmodesmata and developmental regulation of plasmodesmata-based movement are still largely unknown.

There are two distinct pathways for the biogenesis of plasmodesmata (Figure 1B). Plasmodesmata can arise from remnants of endoplasmic reticulum left within the phragmoplast of a dividing cell, and ones formed this way are called primary plasmodesmata. By contrast, secondary plasmodesmata arise independently of cell division; they are inserted into a pre-existing cell wall by a process requiring cell wall thinning and membrane insertion, presumably in conjunction with deposition of secreted cell wall material [9,10]. Although the hormone cytokinin has been shown to increase secondary plasmodesmata production [11], the molecular basis for secondary plasmodesmata biogenesis remains completely unknown. A paper in this issue of *Current Biology* from Burcher-Smith *et al.* [12] makes an important step toward dissecting this pathway. Two genes previously shown to be required for normal *Arabidopsis* embryogenesis and for embryonic symplastic domain establishment — *ISE1* and *ISE2* — have now been shown to be required for negative regulation of secondary plasmodesmata numbers and structure.

The structure of plasmodesmata ranges from simple, characterized by a single sheath of cytoplasm, to complex, characterized by branched, H-shaped, and twinned structures (Figure 1A). These structures also appear to be developmentally regulated, as young tissues commonly have simple plasmodesmata, with complex plasmodesmata arising later, after cell expansion [9]. The molecular basis for forming these distinct plasmodesma morphologies is also unknown, but again, *ise1* and *ise2* might provide clues, as both mutants have higher proportions of the complex plasmodesmata [12].

The identification of *ise1* and *ise2* resulted from the screening of *Arabidopsis* embryos for mutants with defects in the regulation of symplastic domain size [3]. Isolated torpedo-stage embryos were incubated in fluorescent tracers, e.g. a 10 kDa fluorescent-conjugated dextran, which infiltrated through breaks. Normal mid-torpedo embryos establish distinct symplastic domains by reducing their plasmodesmata size exclusion limit; however, *ise* mutants (which stands for Increased Size Exclusion limit) continued to allow free movement of the 10 kDa tracer.

A connection between ISE1 and ISE2 functions and complex plasmodesmata formation came about from an in-depth transmission electron